

Esophagogastric Cancer After Sleeve Gastrectomy: A Systematic Review of Case Reports

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Introduction: Sleeve gastrectomy (SG) is the most commonly performed bariatric procedure. It has been shown that bariatric surgery reduces cancer risk. However, the risk of esophagogastric cancer after SG has not been defined yet and the development of cancer in the esophagus and stomach remains a matter of concern.

Methods: Web of Science, PubMed and Embase databases were searched. Articles that described the diagnosis and management of esophageal or gastric cancer after SG were considered.

Results: Seventeen esophagogastric cancer patients after SG were included. The age of the patients ranged from 21 to 64 years. Tumors were diagnosed after an interval of 33.9 ± 22.8 months from SG (range 4 months–96 months). There were 4 esophageal cancers, 4 gastro-esophageal cancers and 9 gastric cancers; adenocarcinoma was the most frequent tumor histology (88.2%). The most commonly reported symptoms were food intolerance/dyspepsia (50.0%), vomiting/nausea/regurgitation (35.7%). Upper gastrointestinal endoscopy (UGIE) with biopsy was used for diagnosis in most of the patients. Surgery was performed in 10 patients (58.8%), while 4 patients were treated by endoscopic procedures (23.5%). The mean follow-up length was 12.2 months (range 3 months–36 months) and the overall disease-free survival rate was 88.9%.

Conclusion: The development of esophagogastric cancer after SG is still not well defined but it may occur at any time. Preoperative and follow-up UGIE are essential in order to allow for prevention, early diagnosis. Further epidemiologic studies are needed to investigate the post-SG-related risk of esophagogastric cancer development.

Keywords: sleeve gastrectomy, esophageal cancer, gastric cancer, obesity

Introduction

Obesity is one of the major health problems over all the world. Epidemiologic studies have identified high body mass index substantially increases the risk of several cancers, including esophageal cancer, gastric cancer.¹ Some underlying mechanisms, involving adipose tissue inflammation, endocrine and immune alterations, link obesity to cancer development.^{2,3} Bariatric surgery reduces cancer risk along with weight reduction.⁴ However, some studies showed that bariatric surgery is associated with decreased risk of hormone-related cancers, such as breast, endometrium and prostate cancer, whereas gastric bypass might increase the risk of colorectal cancer.⁵ Another study also showed that bariatric surgery is associated with a persistent increase in early-onset colorectal cancer trends.⁶ In fact, a number

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of esophageal and/or gastric cancer after bariatric surgery have been also reported in literature,^{7,8} but the influence of bariatric surgery on the cancers is unclear.

Sleeve gastrectomy (SG) has become the most commonly performed bariatric procedure for the treatment of morbid obesity worldwide.⁹ Its main strengths are technical simplicity, effective resolution of co-morbidities, the low rate of complications, the lack of gastrointestinal anastomosis and malabsorption,¹⁰ but there is concern over some possible complications such as gastroesophageal reflux disease (GERD), which is the main risk factors of esophagogastric cancer. Clinical practice guidelines endorsed by the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) recommend preoperative upper gastrointestinal endoscopy (UGIE) should be considered in possibly all patients eligible for SG,^{11,12} but there are still controversies after surgery. The malignancies after SG are considered rare, but some esophageal or gastric neoplasms are still reported.⁷ It is not clear whether there is a relation between SG and the development of esophagogastric cancers.

The purpose of this systematic review is to summarize epidemiological, histological and clinical feature about esophagogastric cancers after SG, and to determine prevention strategies for high-risk populations.

Materials and Methods

A systematic review was performed using the PubMed, EMBASE and Web of Science databases to identify all English-written published articles about the development of Esophagogastric Cancer after SG up to December 10, 2020. The retrieval strategy was conducted using the following search terms: (neoplasia OR neoplasm OR Tumor* OR Cancer* OR malignancy OR adenocarcinoma) AND (esophageal OR esophagus OR gastric OR stomach) AND (sleeve gastrectomy OR SG OR LSG). Additionally, we also manually screened the references of eligible articles and reviews for other potential articles. All abstracts retrieved were screened and full text acquired for relevant studies. Reviews, comments, conference abstract, nonhuman studies and reports of cancer after bariatric surgery different from SG were excluded. Tumors existing before surgery or at the time of surgery were omitted.

Data extraction from eligible studies was completed independently by two authors (CWH and WYC) using a pre-specified data extraction form: first author, publication year, country, clinical and demographic characteristics of patients' population, type of surgical procedure, and outcomes.

Results

The flow diagram of study selection procedure is displayed in Figure 1. A total of 1068 potentially relevant articles were retrieved in different databases. After removal of duplicate articles, 795 articles were left. Afterwards, we evaluated titles and abstracts, and reviewed full-text. Finally, 17 patients reported cancer arising in the esophagus or the stomach after SG were found in 15 articles.^{13–27} There were 4 esophageal cancers, 4 gastroesophageal cancers and 9 gastric cancers. The characteristics of patients are summarized in Tables 1 and 2. Eleven patients were female (64.7%) and six were male (35.3%); the age of the patients ranged from 21 to 64 years. The body mass index (BMI) prior to SG were available in 16 patients, mean BMI was 47.0 (35.8–75.6) kg/m². Cancer was diagnosed after an interval of 33.9 ± 22.8 months from SG, ranging 4 months to 96 months. The duration of symptoms was reported in 9 patients and ranged from 2 months to 60 months. The BMI at the time of cancer diagnosis was 36.3 (23.8–70.6) kg/m² in 10 patients.

The adenocarcinoma was reported in 4 patients who had not performed the preoperative upper gastrointestinal endoscopy (UGIE). Preoperative detection of *Helicobacter pylori* (Hp) was available only in 9 patients, but HP was positive in one patient. Two patients had chronic gastritis like chronic atrophic gastritis, erosive gastritis before SG. Three cases of cancers after SG occurred in patients who had previously undergone other gastric procedures (gastric pacemaker implantation and intragastric balloon).^{14,18,25} One patient had a history of pancreas transplant (immuno-compromised). Five of the patients were smokers. Other reported risk factors for cancer included family history of upper gastrointestinal cancer, alcohol abuse, immune insufficiency. Most frequent reported comorbidities were obstructive sleep apnea (OSA), type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, GERD, hyperlipidemia, and gastritis (Table 1).

The tumor was located in the distal esophagus in four patients, in the gastroesophageal junction in four patients, in the gastric body and/or antrum in six patients, in the gastric cardia in two patients and in the gastric pylorus in one patient. The adenocarcinoma was the most frequent tumor histology (88.2%), followed by carcinoid (11.7%). The pathological tumor stage was reported in 15 patients and five cases had invaded the adjacent structures or distant metastasis (Table 2).

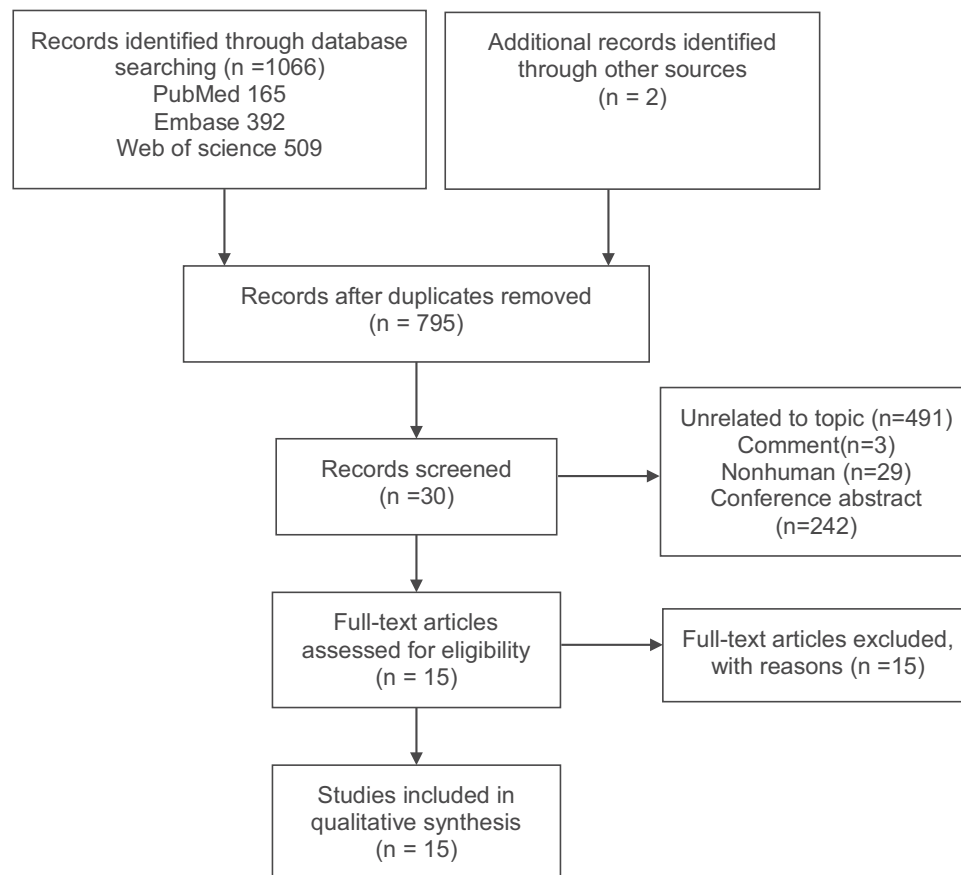


Figure 1 PRISMA flow diagram for selection of studies.

The most commonly reported symptoms were food intolerance/dyspepsia (50.0%), vomiting/nausea/regurgitation (35.7%), abdominal/epigastric pain (35.7%), dysphagia (28.6%), Iron deficiency/anemia (21.4%), asthenia, bloating and back pain (Table 3). Reported examinations for diagnosis and staging were upper gastrointestinal endoscopy (UGE) with biopsy, abdominal CT scan, positron emission tomography (PET). Following cancer diagnosis, surgery was the treatment of choice for 10 patients, while 4 patients were treated by endoscopic procedures. Another 2 patients underwent only chemotherapy and/or radiotherapy. One patient died during completion of diagnostic assessment.

The follow-up was reported in 9 patients; mean follow-up length was 12.2 months (range 3 months– 36 months). Disease-free survival was reported in 8 patients, while one patient died 5 months after surgery.

Discussion

This is the first study to review the available evidence for esophagogastric cancer after SG, summarizing currently available evidence for clinical and demographic characteristics of

cancer patients, risk factors, treatment, outcomes. In the literature, despite it shows that the number of cancer case after SG is small (17 cases), but we can gain the experience in every case to be summarized, allowing for a comprehensive analysis.

The main drawback of SG is that it may induce or aggravate GERD. A recent meta-analysis based on 46 studies totaling 10,718 patients showed that the increase of postoperative GERD after SG was 19% and de novo reflux was 23% and the long-term prevalence of esophagitis was 28% and Barrett's esophagus was 8%.²⁸ However, sleeve gastrectomy associated to anterior fundoplication (D-SLEEVE) can control and/or prevent mild GERD by recreating a functional LES pressure.²⁹ In addition, Pizza et al³⁰ evaluated the clinical-endoscopic results of post-operative One Anastomosis Gastric Bypass(OAGB) in 241 patients and showed that the severity and incidence of esophagitis after OAGB were lower compared to SG. Hence, SG may increase the incidence of GERD. The association between HP infection and GERD remains unclear. A prospective study conducted by Emile et al³¹ showed that morbidly obese patients with Hp infection may

Table I The Basic Condition of the Patient Before Sleeve Gastrectomy

Author (Year)	Nation	Age	Sex	BMI Before SG	Previous UGIE	Endoscopic Findings	HP Infection	Smoking	Comorbidity
Scheepers 2011 ¹³	Netherlands	57	F	51.8	Not	–	–	Yes	OSA, COPD, probably GERD and degenerative joint disease
Angrisani 2014 ¹⁴	Italy	51	F	61	Yes	Significant infiltration of plasma cells in the lamina propria	HP-	-	GERD, OSA, hypertension, dyslipidemia
Erim 2015 ¹⁵	USA	52	F	-	Yes	-	-	-	T2DM, hyperlipidemia, hypertension
Masur 2016 ¹⁶	USA	44	F	38.2	Not	-	HP-	Yes	OSA, Hypertension, T1DM, hyperlipidemia
Sohn 2017 ¹⁷	New Zealand	44	F	42	Not	-	HP-	Not	OSA, hyperlipidemia
Vladimirov 2017 ¹⁸	Germany	47	F	47.7	Yes	Small hiatal hernia and erosive gastritis.	HP-	Yes	COPD
Wright 2017 ¹⁹	Argentina	48	M	48.5	Yes	Absence of reflux or hiatal hernia, no esophagitis or Barrett's esophagus	HP-	-	OSA, hypertension, dyslipidemia, insulin resistance
El Khoury 2018 ²⁰	France	55	F	42	Yes	Barrett's esophagus	-	Not	T2DM, hypertension, dyslipidemia, arthritis
Sista 2018 ²¹	Italy	45	M	42.7	-		-	-	-
Seki 2018 ²²	Japan	64	F	35.3	Yes	Chronic atrophic gastritis	HP-	Not	T2DM
Yamashita 2019 ²³	Singapore	42	F	35.8	Not	-	HP-	Not	GERD, chronic gastritis
Güzel 2020 ²⁴	Cyprus	60	M	38.5	-	-	-	-	T2DM
Muamar 2020 ²⁵	Jordan	26	F	52	Yes	-	HP-	Not	-
Aljarboo 2020 ²⁶	Saudi Arabia	58	F	52	-	-	Hp+	Not	GERD, hypertension, hypothyroidism, bronchial asthma, rheumatoid arthritis
Genco 2020 ²⁷	Italy	54	M	43.1	Yes	No abnormal finding	-	Yes	Hypertension, dyslipidemia, T2DM
Genco 2020 ²⁷	Italy	21	M	75.6	Yes	No abnormal finding	-	Not	OSA
Genco 2020 ²⁷	Italy	39	M	46.3	Yes	No abnormal finding	-	Yes	Hypertension

Abbreviations: UGIE, upper gastrointestinal endoscopy; HP, *Helicobacter pylori*; OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; T1DM or T2DM, type 1 or type 2 diabetes mellitus.

be more prone to develop GERD symptoms. Another study showed HP infection seems not to influence postoperative outcome of SG.³² The main risk factors for esophageal adenocarcinoma are reflux, obesity, smoking and male

sex.³³ A meta-analysis based on 5 studies showed that compared with individuals without reflux symptoms, experiencing symptoms at least weekly increased the odds of developing esophageal adenocarcinoma nearly 5-fold

Table 2 Demographic, Clinical, and Operative Data of the Patient Population

Author (Year)	BMI at Diagnosis of Tumor	Years After SG (Months)	Symptom Duration (Months)	Tumor Location	Tumor Histology	Tumor Stage	Type of Treatment	Follow-Up, Mo
Scheepers 2011 ¹³	-	4	3	Distal esophagus	Adenocarcinoma	T2N1Mx	Chemoradiotherapy	8mo, disease-free survival
Angrisani 2014 ⁴	47	48	-	Body and antrum	Signet-ring cell adenocarcinoma	pT4aN1	Total gastrectomy, Roux-en-Y reconstruction	8mo, disease-free survival
Erim 2015 ¹⁵	-	48	-	Gastric cardia	Carcinoid	-	Submucosal endoscopic dissection	-
Masrur 2016 ¹⁶	31	8	9	Gastroesophageal junction	Adenocarcinoma	pT4bN3a	Robot-assisted extended total gastrectomy, Roux-en-Y reconstruction	8mo, disease-free survival
Sohn 2017 ¹⁷	23.8	24	-	Gastroesophageal junction	Adenocarcinoma	T3N0M0	Chemotherapy + esophagogastrectomy	-
Vladimirov 2017 ¹⁸	-	48	48	Antrum	Adenocarcinoma	pT1bN0	Total gastrectomy, Roux-en-Y reconstruction	24mo, disease-free survival
Wright 2017 ¹⁹	-	60	33	Distal esophagus	Adenocarcinoma	-	Chemoradiotherapy	-
El Khoury 2018 ²⁰	-	36	Several	Distal esophagus	Adenocarcinoma	PTNO	Endoscopic mucosectomy	-
Sista 2018 ²¹	-	42	-	Pylorus	Carcinoid	-	Endoscopic radical resection	36mo, disease-free survival
Seki 2018 ²²	≤29.3	12	-	Antrum	Adenocarcinoma	pT1a	Endoscopic submucosal resection	-
Yamashita 2019 ²³	-	96	-	Body and antrum	Signet-ring cell adenocarcinoma	pT4aN0	Total gastrectomy with lymphadenectomy and omentectomy	12mo, disease-free survival
Güzel 2020 ²⁴	28	36	2	Body	Signet-ring cell adenocarcinoma	-	Total gastrectomy and D2 lymph node dissection	-
Muamar 2020 ²⁵	32.7	63	60	Antrum	Signet-ring cell adenocarcinoma	ypT1N0	Neoadjuvant chemotherapy+ total gastrectomy+ chemotherapy	3mo, disease-free survival

(Continued)

Table 2 (Continued).

Author (Year)	BMI at Diagnosis of Tumor	Years After SG (Months)	Symptom Duration (Months)	Tumor Location	Tumor Histology	Tumor Stage	Type of Treatment	Follow-Up, Mo
Aljarboo 2020 ²⁶	42	48	4	Gastroesophageal junction	Adenocarcinoma	pT2N1M0	Neoadjuvant chemotherapy + distal esophagectomy and total gastrectomy with Roux-en-Y esophagojejunostomy	-
Genco 2020 ²⁷	33.4	24	12	Distal esophagus	Adenocarcinoma	pT2N1M1	Open subtotal esophagectomy with colonic interposition+ adjuvant chemotherapy	5mo, Death
Genco 2020 ²⁷	70.6	22	-	Gastric cardia	Adenocarcinoma	pT3N0M0	Open subtotal esophagectomy with Roux-en-Y esophagojejunostomy= adjuvant chemotherapy	6mo, disease-free survival
Genco 2020 ²⁷	25.0	36		Gastroesophageal junction	Adenocarcinoma	cT3N1M1	-	Death during completion of diagnostic assessment

Table 3 Patients' Symptoms

Symptoms	n (%)
Food intolerance/dyspepsia	7 (50.0%)
Vomiting/Nausea/Regurgitation	5 (35.7%)
Abdominal/epigastric pain	5 (35.7%)
Dysphagia	4 (28.6%)
Iron deficiency/Anemia	3 (21.4%)
Asthenia	2 (14.3%)
Heartburn	2 (14.3%)
Bloating	1 (7.1%)
Back pain	1 (7.1%)

Note: Data are reported as numbers and percentages (%).

(odds ratio [OR], 4.9; 95% confidence interval [95% CI], 3.9–6.2), while daily symptoms increased the odds more than 7-fold (OR, 7.4; 95% CI, 4.9–11.1).³⁴ The pathophysiological pathway of esophageal adenocarcinoma is likely to be chronic gastroesophageal reflux disease, causing metaplasia from the native squamous cell mucosa to a specialized columnar epithelium (Barrett's esophagus), which develops into esophageal cancer.³⁵ In this review, three patients did not undergo UGIE before SG and two of the patients with a history of smoking after SG developed cancer in four months and eight months post-operation. From this point, we can infer that these patients had been probably present early or premalignant esophageal lesions before SG. One patient developed GERD symptoms 15 months after SG, but he refused to be studied and was lost to follow-up.¹⁹ Another cancer patient also developed GERD after SG was the presence of Hp infection.²⁶ Therefore, it is vital to thoroughly screen obese patients before SG to rule out the presence of potential esophageal lesions. Those with GERD is present, gastric bypass should be recommended instead of SG. More importantly, considering the risks of postoperative GERD, esophagitis, and Barrett's esophagus, UGIE is important to use to monitor esophageal lesions of patients during long-term follow-up after SG.

The pathological mechanism for the development of cancer in remnant stomach remains unclear. Some important risk factors are infection of the gastric mucosa by HP, previous chronic gastritis, a family history of upper gastrointestinal cancer, obesity, smoking, and previous gastric surgeries.³⁶ In this study, two patients had chronic gastritis,^{18,22} and one patient was a pancreas transplant case (immunocompromised),¹⁶ which augment the chance of developing gastric cancer. In addition, intestinal metaplasia and dysplasia will also increase risk of cancer in

remnant stomach. The most important for early detection of these lesions is the use of UGIE during follow-up.

Carcinoid tumor is the most common neuroendocrine tumor of the stomach. Gastric carcinoids are regarded as rare but their incidence has gradually increased over the past decades, due to environmental factors, diet alterations, longer life expectancy and increased upper endoscopy screening.^{37,38} This incidence is higher in patients undergoing upper gastro-intestinal endoscopic evaluations before bariatric surgery.¹⁵ Furthermore, obesity may increase the prevalence of malignant gastric carcinoid tumors.³⁹ The underlying mechanisms behind above higher incidence may attribute to hormonal changes that happen in obese people. Masuda et al conducted an animal study on obese diabetic rats undergone SG and found antral G cells hyperplasia led to hypergastrinemia.⁴⁰ Hypergastrinemia plays a major role in pathogenesis of gastric carcinoid tumor.³⁸ Hence, the risk of gastric carcinoid tumor may be increased after SG. However, only two cases of gastric carcinoid were found after SG, so there is not conclusive evidence to support the hypothesis of a higher incidence of gastric carcinoid after SG. Therefore, it is extremely important to detect this type of tumor early through strict follow-up.

The diagnosis of esophagogastric cancer after SG is usually late since these patients underwent UGIE when they were present with the new onset of symptoms. The vague or absent signs and symptoms developed by patients might be the reasons of a delayed diagnosis. Furthermore, upper gastrointestinal symptoms such as food intolerance/dyspepsia and vomiting/nausea/regurgitation are usually attributable to bariatric surgery itself and are for this reason often overlooked. In this literature, the duration of symptoms ranged from 2 months to 60 months, which meant that many patients had symptoms after surgery, but they did not take it seriously. Although these new symptoms are not specific, attention must be paid by doctors and patients. More importantly, the follow-up UGIE after SG is necessary, especially for certain patients (males, smokers, those with upper GI symptoms, those with GERD, family history of upper GI cancer, evidence of previous H pylori)

Conclusion

Data on the development of esophagogastric cancer after SG are scarce and the real incidence is unknown, but it may occur at any time. Because of the increasing number of SG, surgeons should be aware of this potential event. Preoperative and follow-up UGIE are essential in order to

allow for prevention, early diagnosis. Further epidemiologic studies are needed to investigate the post-SG-related risk of esophagogastric cancer development.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

A Statement of Formal Consent

For this type of study, formal consent is not required.

Disclosure

The authors declare that they have no conflict of interest.

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